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Estimation of the additive hazards model with current status data in the presence of informative censoring

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The additive hazards model is one of the most commonly used regression models in the analysis of failure time data and many methods have been developed for its inference under various situations. This paper discusses the situation where one faces current status data and also there exists informative censoring or when the failure time of interest and the observation process are correlated. Several authors have discussed the problem and in particular, Zhang et al. (2005) and Zhao et al. (2015) proposed an estimating equation-based approach and a copula model-based method, respectively. However, the former may not be efficient and the latter needs some restrictive assumptions. To address these, we propose a sieve maximum likelihood estimation approach that can be more efficient and also does not require the assumption above. For the implementation of the method, an EM algorithm is developed and the asymptotic properties of the resulting estimators are established. The numerical results suggest that the proposed method works well in practical situations and an application is provided.

Keywords and phrases: Current status data, EM algorithm, Informative censoring.

1. INTRODUCTION

This paper discusses regression analysis of current status data arising from the additive hazards model. By current status data, we usually mean that each study subject is observed only once and thus the failure time of interest is known only to be either smaller or greater than the observation time. In other words, the observation on the failure time is either left- or right-censored instead of being observed exactly. One type of studies that usually yield current status data is cross-sectional studies, which are commonly used in many fields including demographical studies, epidemiological survey, and tumorigenicity experiments (Finkelstein and Schoenfeld, 1989; Jewell and Van Der Laan, 1995; Sun, 2006).

To give an example of current status data, consider a tumorigenicity experiment and in this situation, the failure time of interest is usually the time to tumor onset and each study animal is only observed at the death or sacrifice. In other words, on the tumor onset, only the information about the presence or absence of a tumor at the death is available and thus the time to tumor onset is only known to be either smaller or larger than the death or sacrifice time. That is, only current status data are observed. If the tumor is nonlethal, then it is usually reasonable to assume that the tumor time and death time are independent. However, since most of tumors are between lethal and non-lethal, we cannot treat them independent and in other words, we have informative or dependent current status data.

Many authors have discussed regression analysis of current status data (Finkelstein and Schoenfeld, 1989; Hu et al., 2009; Jewell and Van Der Laan, 1995; Lin et al., 1998; Sun, 1999; Martinussen and Scheike, 2002; Wen and Chen, 2011). However, most of the proposed methods are for the situations where the failure time of interest and the observation time can be assumed to be completely or conditionally independent given covariates. Several methods have also been developed for regression analysis of informative current status data (Chen et al., 2012; Li et al., 2017; Ma et al., 2015). In particular, Zhang et al. (2005) and Zhao et al. (2015) investigated the problem for the situation where the failure time of interest follows the additive hazards model and proposed an estimating equation-based estimation procedure and a copula model-based method. However, the former may not be efficient and the latter needs to assume that the underlying copula model and the association parameter between the failure time and the observation time are known, which may not be true in reality. To address these, we will develop an efficient sieve maximum likelihood estimation approach that does not require the assumption above.

In the following, we will first describe some notation, models and some assumptions that will be used throughout the paper along with the resulting likelihood function in Section 2. A sieve maximum likelihood estimation procedure is presented in Section 3 with the use of some spline functions to approximate the unknown baseline cumulative hazard function. For the implementation of the proposed procedure, an EM algorithm is developed and the resulting estimators of regression parameters are shown to be

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consistent and follow asymptotically a normal distribution. Section 4 presents some numerical results from a simulation study conducted for the assessment of the finite sample properties of the proposed method, and they indicate that the method works well in practical situations and is more efficient than that given in Zhang et al. (2005) as expected. An application from a tumorigenicity experiment is provided in Section 5 and Section 6 contains some discussion and concluding remarks.

2. NOTATION, MODELS AND ASSUMPTIONS

Consider a failure time study that involves n independent subjects and only gives current status data. For subject i, let T_i denotes the failure time of interest and C_i the observation time that may be related to T_i, $i = 1, \ldots, n$. For the tumorigenicity example, T_i and C_i represent the tumor onset and animal death times, respectively. Also for subject i, suppose that there exist a vector of covariates, denoted by Z_i, and a latent variable b_i with mean zero and variance η. Both Z_i and b_i will be assumed to be time-independent and some comments on this will be given below. For the covariate effect on the T_i's, we will assume that given Z_i and b_i, T_i follows the additive hazards frailty model given by

$$\lambda_i(t|Z_i, b_i, s \leq t) = \lambda_1(t) + b_i + \beta' Z_i \tag{1}$$

(Lin et al., 1998; Zhang et al., 2005). In the above, $\lambda_1(t)$ is an unknown baseline hazard function and β represents the vector of regression parameters.

In this paper, we will focus on the situation where the C_i's may depend on both the T_i's and the covariate. For this, by following Zhang et al. (2005), we will assume that given Z_i and b_i, C_i follows the proportional hazards frailty model specified by

$$\lambda_i^c(t|Z_i, b_i, s \leq t) = \lambda_2(t)\exp\{\gamma' Z_i + b_i\}, \tag{2}$$

where $\lambda_2(t)$ is an unknown baseline hazard function and γ denotes the vector of regression parameters. Of course, instead of the model (2), one may employ other models such as the model (1) to describe the effects of covariates on the C_i's and some comments on this will be given below. In the following, it will be assumed that given the b_i's, the T_i's and the C_i's are independent.

For any study giving current status data, in addition to C_i, there may exist another observation or censoring time C_i^c that is independent of T_i such as the sacrifice time in a tumorigenicity experiment. In this case, of course, one only observes the smaller of the two time points C_i and C_i^c. Define $C_i^* = \min(C_i, C_i^c)$, $\Delta_i = I(C_i^* = C_i)$ and $\delta_i = I(T_i \leq C_i^*)$. Let $\Lambda_1(t) = \int_0^t \lambda_1(s)ds$, $\Lambda_2(t) = \int_0^t \lambda_2(s)ds$, $\mathrm{B}_i(t) = b_i t$, and $Z_i^*(t) = Z_i t$. Also define $S(t) = \exp\{-\Lambda_1(t) - \mathrm{B}_i(t) - \beta' Z_i^*(t)\}$, $S^c(t) = \exp\{-\Lambda_2(t)\exp\{\gamma' Z_i + b_i\}\}$, and $f^c(t) = S^c(t)\lambda_2(t)\exp\{\gamma' Z_i + b_i\}$. Then the observed data consist of $\{(C_i^*, \Delta_i, \delta_i, Z_i);\ i = 1, \ldots, n\}$ and the resulting likelihood function has the form

$$\begin{aligned}
&L(\beta, \gamma, \eta, \lambda_1, \lambda_2) \\
&= \prod_{i=1}^n \int_{-\infty}^{\infty} \{[(1 - S(c_i^*))f^c(c_i^*)]^{\delta_i}[S(c_i^*)f^c(c_i^*)]^{1-\delta_i}\}^{\Delta_i} \\
&\times\{[(1 - S(c_i^*))S^c(c_i^*)]^{\delta_i}[S(c_i^*)S^c(c_i^*)]^{1-\delta_i}\}^{1-\Delta_i} \\
&\times f(b_i;\eta)db_i(s) \\
&= \prod_{i=1}^n \int_{-\infty}^{\infty} [1 - S(c_i^*)]^{\delta_i}[S(c_i^*)]^{1-\delta_i}[S^c(c_i^*)]^{1-\Delta_i} \\
&\times[f^c(c_i^*)]^{\Delta_i} f(b_i;\eta)db_i \\
&= \prod_{i=1}^n \int_{-\infty}^{\infty} [1 - S(c_i^*)]^{\delta_i}[S(c_i^*)]^{1-\delta_i} S^c(c_i^*) \qquad (3) \\
&\times[\lambda_2(c_i^*)\exp\{\gamma' Z_i(c_i^*) + b_i(c_i^*)\}]^{\Delta_i} f(b_i;\eta)db_i\,,
\end{aligned}$$

where $f(b_i;\eta)$ denotes the density function of the b_i's assumed to be known up to η. In the next section, we will discuss the maximization of the likelihood function above.

3. SIEVE MAXIMUM LIKELIHOOD ESTIMATION

Now we discuss estimation of the regression parameters β and γ as well as others by employing the maximum likelihood estimation approach. For this, we will develop an EM algorithm for the maximization and then establish the asymptotic properties of the resulting estimators. For the simplicity of the presentation of the EM algorithm, we will first consider the situation where $C_i^c = \infty$ for all i or there is no censoring on the C_i's.

3.1 Estimation without censoring times

In this subsection, we will assume that the observed data have the form $\{(C_i, \delta_i = I(T_i \leq C_i), Z_i);\ i = 1, \ldots, n\}$. Then the likelihood function given in (3) reduces to

$$\begin{aligned}
&L(\beta, \gamma, \eta, \lambda_1, \lambda_2) \\
&= \prod_{i=1}^n \mathrm{P}(C_i = c_i, \delta_i = 1|Z_i)^{\delta_i}\mathrm{P}(C_i = c_i, \delta_i = 0|Z_i)^{1-\delta_i} \\
&= \prod_{i=1}^n \int_{-\infty}^{\infty} [1 - S(c_i)]^{\delta_i}[S(c_i)]^{1-\delta_i} f^c(c_i) f(b_i;\eta)db_i\,.
\end{aligned}$$

It is apparent that in addition to the integration, another factor that makes the maximization of $L(\beta, \gamma, \eta, \lambda_1, \lambda_2)$ difficult is the involvement of two unknown function $\Lambda_1(t)$ and $\Lambda_2(t)$. As seen below, the function $\Lambda_2(t)$ can be estimated relatively easily but not the function $\Lambda_1(t)$. To address this, by following Ma et al. (2015), Zhao et al. (2015) and others, we propose to employ the sieve approach to approximate

$\Lambda_1(t)$ by monotone splines (Ramsay, 1988) as

$$\Lambda_{1n}(t) = \sum_{l=1}^{s+k_n} \alpha_l \, I_l(t) \, .$$

In the above, $\{I_l(t), l = 1, \ldots, s + k_n\}$ are some integrated spline basis functions with the order s and k_n and the α_l's are nonnegative coefficients that ensure the monotonicity of $\Lambda_{1n}(t)$. In the numerical studies below, we used I-spline functions.

To develop the EM algorithm, let $\theta = (\beta', \gamma', \eta, \Lambda_1, \Lambda_2)$, representing all unknown parameters. First note that the likelihood function above can be rewritten as

$$L(\theta) = \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} L_1(\beta, \alpha) L_2(\gamma, \lambda_2) L_3(\eta) db_1 \cdots db_n \, ,$$

where $\alpha = (\alpha_1, ..., \alpha_{s+k_n})'$,

$$\begin{aligned} L_1(\theta_1) &= \prod_{i=1}^{n} (1 - \exp\{-\Lambda_1(c_i) - \mathrm{B}_i(c_i) - \beta' Z_i^*(c_i)\})^{\delta_i} \\ & \quad \exp\{-(1-\delta_i)(\Lambda_1(c_i) + \mathrm{B}_i(c_i) + \beta' Z_i^*(c_i))\} \, , \\ L_2(\theta_2) &= \prod_{i=1}^{n} S^c(c_i) \lambda_2(c_i) \exp\{\gamma' Z_i + b_i\} \, , \end{aligned}$$

and

$$L_3(\eta) = \prod_{i=1}^{n} f(b_i; \eta)$$

with $\theta_1 = (\beta, \alpha)$ and $\theta_2 = (\gamma, \lambda_2)$. Define $L_c(\theta) = L_1(\theta_1) \, L_2(\theta_2) \, L_3(\eta)$ and let $\hat{\theta}^{(m)}$ denote the estimator of θ obtained in the mth iteration. To obtain $\hat{\theta}^{(m+1)}$, note that we have that

$$\begin{aligned} & E_{b_i}[\log L_c(\beta, \gamma, \lambda_1, \lambda_2, \eta | \hat{\theta}^{(m)})] = E_{b_i}[\log L_1(\beta, \alpha | \hat{\theta}^{(m)})] \\ & + E_{b_i}[\log L_2(\gamma, \lambda_2 | \hat{\theta}^{(m)})] + E_{b_i}[\log L_3(\eta | \hat{\theta}^{(m)})] \\ & = E_{b_i}[\log L_1(\theta_1 | \hat{\theta}^{(m)})] + E_{b_i}[\log L_2(\theta_2 | \hat{\theta}^{(m)})] \\ & + E_{b_i}[\log L_3(\theta_3 | \hat{\theta}^{(m)})] \, , \end{aligned}$$

where $\theta_3 = \eta$. Furthermore, it can be shown that

$$\begin{aligned} & E_{b_i}[\log L_1(\theta_1 | \hat{\theta}^{(m)})] \\ & = \sum_{i=1}^{n} \{\delta_i E_{b_i}[\log(1 - \exp(-\Lambda_1(c_i) - \mathrm{B}_i(c_i) - \beta' Z_i^*(c_i)) | \hat{\theta}^{(m)}] \\ & - (1 - \delta_i) E_{b_i}[\Lambda_1(c_i) + \mathrm{B}_i(c_i) + \beta' Z_i^*(c_i) | \hat{\theta}^{(m)}]\} \, . \end{aligned}$$

It follows that one can calculate $\hat{\beta}^{(m+1)}$ and $\{ \hat{\alpha}_l^{(m+1)}, l = 1, \ldots, s + k_n \}$ by solving the following score equations

$$\begin{aligned} S_\beta(\theta_1) &= \frac{\partial E_{b_i}[\log L_1(\theta_1 | \hat{\theta}^{(m)})]}{\partial \beta} \\ &= \sum_{i=1}^{n} Z_i^*(c_i) \times \\ & \quad E_{b_i}[\frac{\delta_i}{1 - \exp(-\Lambda_1(c_i) - \mathrm{B}_i(c_i) - \beta' Z_i^*(c_i))} - 1 | \hat{\theta}^{(m)}] \\ &= 0 \end{aligned} \tag{4}$$

and

$$\begin{aligned} S_{\alpha_l}(\theta_1) &= \frac{\partial E_{b_i}[\log L_1(\theta_1 | \hat{\theta}^{(m)})]}{\partial \alpha_l} \\ &= \sum_{i=1}^{n} I_l(c_i) \times \\ & \quad E_{b_i}[\frac{\delta_i}{1 - \exp(-\Lambda_1(c_i) - \mathrm{B}_i(c_i) - \beta' Z_i^*(c_i))} - 1 | \hat{\theta}^{(m)}] \\ &= 0 \, . \end{aligned} \tag{5}$$

To obtain the updated estimation of γ, by treating Λ_2 as a piecewise constant function at the times C_i's, $\hat{\gamma}^{(m+1)}$ can be obtained by solving the following score equation

$$\begin{aligned} S_\gamma &= \frac{\partial E_{b_i}[\log L_2(\theta_2 | \hat{\theta}^{(m)})]}{\partial \gamma} \\ &= \sum_{i=1}^{n} \int_0^\infty \{Z_i - \bar{Z}(t; \gamma)\} dN_i(t) = 0 \, , \end{aligned} \tag{6}$$

where $N_i(t) = I\{C_i \leq t\}$, $Y_i = I\{C_i \geq t\}$, and

$$\bar{Z}(t; \gamma) = \frac{\sum_{i=1}^{n} Y_i(t) Z_i \exp(Z_i' \gamma) E_{b_i}(e^{b_i} | \hat{\theta}^{(m)})}{\sum_{i=1}^{n} Y_i(t) \exp(Z_i' \gamma) E_{b_i}(e^{b_i} | \hat{\theta}^{(m)})} \, .$$

Given $\gamma^{(m+1)}$, the updated estimator $\hat{\Lambda}_2^{(m+1)}$ of Λ_2 can be obtained by the Breslow-type estimator

$$\hat{\Lambda}_2^{(m+1)}(t) = \sum_{i=1}^{n} \int_0^t \frac{dN_i(\mu)}{\sum_{i=1}^{n} Y_i(\mu) \exp(Z_i' \gamma^{(m+1)}) E_{b_i}(e^{b_i} | \hat{\theta}^{(m)})} \, . \tag{7}$$

Furthermore, one can obtain an estimator of η by maximizing $E_{b_i}(\log L_3(\eta) | \hat{\theta}^{(m)})$.

3.2 Estimation with censoring times

Now suppose that both C_i and C_i^c can exist or one can observe either C_i or C_i^c. In this case, the likelihood function is given in (3) and for estimation of the parameters β and α, one can easily obtain the estimating equations similar to (4) and (5). For estimation of γ, one can also derive a score equation similar to (6) as

$$S_\gamma = \sum_{i=1}^{n} \int_0^\infty \{Z_i - \bar{Z}^*(t; \gamma)\} dN_i^*(t) = 0 \, , \tag{8}$$

where $N_i^*(t) = I\{C_i^* \le t, \Delta_i = 1\}$, $Y_i^* = I\{C_i^* \ge t\}$ and

$$\bar{Z}^*(t;\gamma) = \frac{\sum_{i=1}^n Y_i^*(t) Z_i \exp(Z_i'\gamma) E_{b_i}(e^{b_i}|\hat{\theta}^{(m)})}{\sum_{i=1}^n Y_i^*(t) \exp(Z_i'\gamma) E_{b_i}(e^{b_i}|\hat{\theta}^{(m)})}.$$

Given $\gamma^{(m+1)}$, the updated estimator $\hat{\Lambda}_2^{(m+1)}$ of Λ_2 can again be obtained by the following Breslow-type estimator

(9)
$$\hat{\Lambda}_2^{(m+1)}(t) = \sum_{i=1}^n \int_0^t \frac{dN_i^*(\mu)}{\sum_{i=1}^n Y_i^*(\mu)\exp(Z_i'\gamma^{(m+1)}) E_{b_i}(e^{b_i}|\hat{\theta}^{(m)})}.$$

Let J be an integer. Then all EM steps discussed above can be summarized as follows.

Step 1. Choose an initial estimate $\theta^{(0)}$.
Step 2. At the $(m+1)$th iteration, first generate the random variables $\{ b_{ij};\ j = 1, \cdots, J, i = 1, \cdots, n \}$ from the density function $f(b_i;\eta)$, and then compute the conditional expectations described above under $\hat{\theta}^{(m)}$ by using the Monte Carlo method. More specifically, for any arbitrary function $h(b_i)$, we approximate $E\{ h(b_i)|\hat{\theta}^{(m)} \}$ by

$$E\{h(b_i)|\hat{\theta}^{(m)}\} \approx \frac{\sum_{j=1}^J h(b_{ij})\psi_i(b_{ij};\hat{\theta}^{(m)})}{\sum_{j=1}^J \psi_i(b_{ij};\hat{\theta}^{(m)})}, \tag{10}$$

where $\psi_i(b_{ij};\hat{\theta}^{(m)}) = [1 - S(c_i)]^{\delta_i}[S(c_i)]^{1-\delta_i} f^c(c_i)$ for the case with no censoring and $\psi_i(b_{ij};\hat{\theta}^{(m)}) = [1 - S(c_i^*)]^{\delta_i}[S(c_i^*)]^{1-\delta_i}[S^c(c_i^*)]^{1-\Delta_i}[f^c(c_i^*)]^{\Delta_i}$ otherwise.
Step 3. Obtain $\hat{\beta}^{(m+1)}$ from equation (4) by using the Broyden-Fletcher-Goldfarb-Shanno algorithm with $\alpha_l = \alpha_l^{(m)}$.
Step 4. Compute $\hat{\alpha}^{(m+1)}$ from equation (5) by applying the quasi-Newton method given $\hat{\beta}^{(m+1)}$.
Step 5. Update $\hat{\gamma}^{(m+1)}$ by solving the equation (8) by using the Newton-Raphson algorithm.
Step 6. Obtain $\hat{\Lambda}_2^{(m+1)}$ from (9) by replacing γ with $\hat{\gamma}^{(m+1)}$.
Step 7. Determine $\hat{\eta}^{(m+1)} = \text{argmax} E_{b_i}(\log L_3(\eta)|\hat{\theta}^{(m)})$.
Step 8. Repeat Steps 2–7 until the convergence.

Let $\hat{\theta}_n = (\hat{\beta}', \hat{\gamma}', \hat{\eta}, \hat{\Lambda}_{1n}, \hat{\Lambda}_2)$ denote the estimator of θ defined above. In the Appendix, we will show that they are consistent and also $\hat{\beta}$ and $\hat{\gamma}$ are asymptotically normally distributed and semi-parametrically efficient. It is apparent that to implement the sieve maximum likelihood estimation procedure described above, one needs to choose s and k_n. The degree s should be usually decided by the smoothness of the true baseline cumulative hazard function and many authors have investigated it and suggested that 1, 2 or 3 is often good enough. A general criterion for k_n, the number of knots, is to set it to be around $n^{1/3}$ and in practice, a simple way for their selections is to try different values and compare the obtained estimators. As an alternative, one can also perform a grid search and employ the AIC criterion by choosing the values of s and k_n that give the smallest AIC.

For the estimation of the covariance matrix of $\hat{\beta}$ and $\hat{\gamma}$, a common approach is to use the Louis's Formula but it would be computationally intensive for the situation considered here. Corresponding to this and by following Wen and Chen (2011) and others, we propose to employ the profile likelihood approach. Suppose that we want to estimate the covariance matrix of $\hat{\beta}$. First define the profile likelihood function $PL_n(\beta)$ as the maximum of the likelihood function $L(\beta, \gamma, \eta, \lambda_1, \lambda_2)$ over all other parameters with fixed β. Let p denote the dimension of β and e_i be a p-dimensional vector with 1 in the ith position and zero elsewhere. Then one can estimate the (i, j) element of the efficient Fisher information matrix corresponding to β by

$$(\hat{I_n})_{ij} = -\frac{\log PL_n(\hat{\beta} + \rho_n e_i + \rho_n e_j) - \log PL_n(\hat{\beta} + \rho_n e_i)}{n\,{\rho_n}^2}, \\ -\frac{\log PL_n(\hat{\beta} + \rho_n e_j) + \log PL_n(\hat{\beta})}{n\,{\rho_n}^2},$$

where $\rho_n = O_p(n^{-1/2})$ is a constant. It follows that the covariance matrix of $\hat{\beta}$ can be estimated by $(\,(\hat{I_n})_{ij}\,)^{-1}$. Similarly one can estimate the covariance matrix of $\hat{\gamma}$ and the numerical studies below suggest that this method seems to work well.

4. A SIMULATION STUDY

In this section, we report some results obtained from a simulation study conducted to assess the finite sample performance of the sieve maximum likelihood estimation procedure proposed in the previous sections. In the study, we assume that there exists one covariate Z_i following the Bernoulli distribution with the success probability of 0.5. To generate the observed data, we first generated the latent variables b_i's from the truncated normal distribution with mean 0 and variance $\eta = 0.1$ or the uniform distribution over $(-0.5, 05)$. Note that the truncated normal distribution was used to make sure that $S(t) = \exp\{-\Lambda_1(t)^{(m)} - B_i(t) - \beta^{(m)} Z_i^*(t)\}$ lies between $[0, 1]$ and $B_i(t) = \int_0^t b_i ds > -\Lambda_1(t)^{(m)} - \beta^{(m)} Z_i^*(t)$. Given the covariates and latent variables, the failure times T_i's and the observation times C_i's were then generated under models (1) and (2) with $\lambda_1(t) = \lambda_2(t) = 1$. The independent observation or censoring times C_i^c's were set to be the constant τ, which was chosen to give the desired censoring percentage. For the results given below, we took $s = 3$, $k_n = 5$ and $J = 100$ and chose the interior knots to be equally spaced time points between the minimum and maximum real observation times. Also the results given below are based on the sample size $n = 200$ or 400 with 1000 replications.

Table 1 presents the results on estimation of β and γ with the true value of (β, γ) being $(0, 0)$, $(0, 0.2)$, $(0.2, 0.2)$ or $(0.5, 0.5)$, $n = 200$, the b_i's generated from the truncated normal distribution and the censoring percentage on the C_i's being 20%. The results include the average of the estimates (Mean), the sample standard error (SSE) of the estimates, the average of the estimated standard errors (SEE), and the 95% empirical coverage probabilities (CP). For comparison, we also obtained the results given by the estimating equation approach proposed by Zhang et al. (2005). One can see that the proposed estimator seems to be unbiased and the proposed standard error estimation appears to be close to the sample standard deviations and works well. Also the empirical coverage probabilities are very close to the nominal level and indicate that the normal approximation to the distribution of the proposed estimator is reasonable. In addition, the proposed estimator is clearly more efficient than that given in Zhang et al. (2005).

The results given in Table 2 were obtained under the same set-up as with Table 1 but with the censoring percentage on the C_i's being 60%, while Table 3 presents the results also obtained under the same set-up as with Table 1 but with the b_i's generated from the uniform distribution. Note that in Table 2, we also obtained and include the results with $n = 400$. It is apparent that the results in both tables gave similar conclusions as with Table 1 and again indicate that the proposed method seems to work well. In addition, as expected, the results became better when the sample size increased, and the proposed estimation procedure seems to work well with respect or robust to different frailty distributions. To further investigate the normal distribution approximation, we obtained the quantile plots of the standardized $\hat{\beta}$ and $\hat{\gamma}$ against the standard normal distribution. Figure 1 displays the plots corresponding to the situation with $(\beta, \gamma) = (0, 0)$, $(0.2, 0.2)$ or $(0.5, 0.5)$ in Table 1 and again suggests that the normal approximation seems to be appropriate.

5. AN APPLICATION

Now we apply the methodology proposed in the previous sections to a tumorigenicity experiment discussed by Zhang et al. (2005) among others with the data given in Tables 1 and 2 of Lindsey and Ryan (1994). The experiment, conducted at the National Center for Toxicological Research, randomly assigned female mice to either a control group or one of seven dose groups of the known carcinogen 2-acetylaminofluorene. Also it was designed to have eight interim sacrifice times and a terminal sacrifice at 33 months. By following Lindsey and Ryan (1994) and Zhang et al. (2005), in the analysis below, we will consider a subset of data from one room, consisting of 671 animals in the control group (387) and high-dose group (284), with the focus on both lung and bladder tumors for each animal. On the lung tumor onset time, 121 mice gave left-censored observations, 69 from the control group and 52 from the high-dose group. In contrasts, on the bladder tumor onset time, 124 left-censored observations were obtained with only 13 from the control group and 111 from the high-dose group. As mentioned above, in the analysis below, we will treat the natural death time as C_i and the terminal sacrifice time as C_i^c.

For the analysis, define $Z_i = 0$ for the mice in the control group and $Z_i = 1$ otherwise. Table 4 presents the estimated dose effects given by the application of the proposed estimation procedure to both lung and bladder tumors, respectively, along with the estimated standard errors and the p-values for testing no group or dose effect. Note that here we chose $s = 3$ and set k_n being from 3 to 10 to allow for both the sufficient model flexibility and less computational burden. Also the AIC values were calculated for comparing different models and given in the table, and the smallest AIC value was given by $k_n = 3$ for both lung tumor and bladder tumor. On the other hand, all AIC values are quite close to each other and the estimation results are also consistent with respect to k_n.

One can see from Table 4 that with respect to the dose effect on the death rate, the proposed method yielded $\hat{\gamma} = 0.482$ and 0.471 with $k_n = 3$ for the lung and bladder tumors with the estimated standard errors being 0.187 and 0.189, respectively. These correspond to the p-values of 0.01 and 0.013 for testing $\gamma = 0$ and indicate that the animals in the high-dose group had significantly higher death rates than those in the control group. With respect to the dose effect on the tumor growth rate and $k_n = 3$, the proposed method gave $\hat{\beta} = 0.014$ and 0.292 for the lung and bladder tumors with the estimated standard errors being 0.019 and 0.031, respectively. They suggest that there existed significant dose effect on the bladder tumor growth rate, but the lung tumor risks between the two dose groups did not seem to be significantly different. In the analysis here, we also tried different values for s and obtained similar results, and the conclusions here are similar to those given by Lindsay and Ryan (1994) and Zhang et al. (2005).

6. DISCUSSION AND CONCLUDING REMARKS

This paper discussed regression analysis of current status data arising from the additive hazards frailty model in the presence of informative observation or censoring time and for the problem. A sieve maximum likelihood estimation procedure was proposed with the use of I-spline functions. Also for the implementation of the method, an EM algorithm was developed and the resulting estimators of regression parameters were shown to be consistent and asymptotically normal. In addition, the simulation study performed indicates that it works well for practical situations and as expected, the proposed approach is more efficient than that given in Zhang et al. (2005).

As mentioned above, the focus here has been on the additive hazards model or the current status data arising from the additive hazards model, and it is clear that sometimes

Table 1. Simulation results on estimation of regression parameters, including the averages of the estimates (Mean), the sample standard error (SSE), the average of the estimated standard errors (SEE) and the 95% *empirical coverage probabilities (CP) with 20% censoring and* $n = 200$

		Method	β				γ			
β	γ		Mean	SSE	SEE	CP	Mean	SSE	SEE	CP
0	0	Proposed	-0.004	0.245	0.233	0.948	0.002	0.167	0.159	0.943
		Zhang et.al	0.027	0.610	0.589	0.962	-0.002	0.287	0.286	0.958
0	0.2	Proposed	-0.005	0.241	0.232	0.947	0.197	0.144	0.135	0.945
		Zhang et.al	0.026	0.598	0.571	0.958	0.177	0.287	0.273	0.953
0.2	0.2	Proposed	0.220	0.242	0.240	0.944	0.204	0.169	0.159	0.942
		Zhang et.al	0.227	0.690	0.660	0.953	0.175	0.291	0.286	0.952
0.5	0.5	Proposed	0.530	0.276	0.272	0.942	0.501	0.168	0.160	0.943
		Zhang et.al	0.532	0.826	0.777	0.950	0.439	0.296	0.287	0.943

Table 2. Simulation results on estimation of regression parameters, including the averages of the estimates (Mean), the sample standard error (SSE), the average of the estimated standard errors (SEE) and the 95% *empirical coverage probabilities (CP) with 60% censoring and* $n = 200$ *or* 400

				β				γ			
β	γ	n		Mean	SSE	SEE	CP	Mean	SSE	SEE	CP
0	0	200	Proposed	-0.002	0.268	0.253	0.926	-0.002	0.232	0.225	0.947
			Zhang et.al	-0.037	2.747	2.674	0.952	-0.013	0.449	0.435	0.944
		400	Proposed	0.001	0.215	0.192	0.942	0.001	0.187	0.181	0.942
			Zhang et.al	0.033	1.929	1.867	0.948	0.005	0.306	0.303	0.95
0.2	0.2	200	Proposed	0.210	0.295	0.279	0.938	0.207	0.233	0.226	0.938
			Zhang et.al	0.218	3.07	2.963	0.946	0.176	0.449	0.435	0.948
		400	Proposed	0.206	0.242	0.220	0.943	0.203	0.188	0.183	0.941
			Zhang et.al	0.354	2.123	2.063	0.959	0.195	0.306	0.303	0.95
0.5	0.5	200	Proposed	0.516	0.347	0.357	0.948	0.516	0.237	0.23	0.954
			Zhang et.al	0.797	3.718	3.486	0.942	0.469	0.461	0.44	0.948
		400	Proposed	0.508	0.293	0.285	0.945	0.508	0.191	0.187	0.951
			Zhang et.al	0.847	2.468	2.422	0.952	0.478	0.304	0.306	0.953

Table 3. Simulation results on estimation of regression parameters, including the averages of the estimates (Mean), the sample standard error (SSE), the average of the estimated standard errors (SEE) and the 95% *empirical coverage probabilities (CP) with the uniform frailty distribution,* 20% *censoring and* $n = 200$

		Method	β				γ			
β	γ		Mean	SSE	SEE	CP	Mean	SSE	SEE	CP
0	0	Proposed	0.006	0.135	0.132	0.948	0.003	0.145	0.136	0.944
		Zhang et.al	0.029	0.598	0.573	0.957	-0.002	0.273	0.271	0.956
0.2	0.2	Proposed	0.179	0.147	0.143	0.946	0.201	0.145	0.137	0.943
		Zhang et.al	0.168	0.675	0.654	0.954	0.179	0.286	0.281	0.951
0.5	0.5	Proposed	0.468	0.163	0.159	0.945	0.499	0.147	0.139	0.945
		Zhang et.al	0.467	0.813	0.762	0.952	0.446	0.292	0.284	0.948

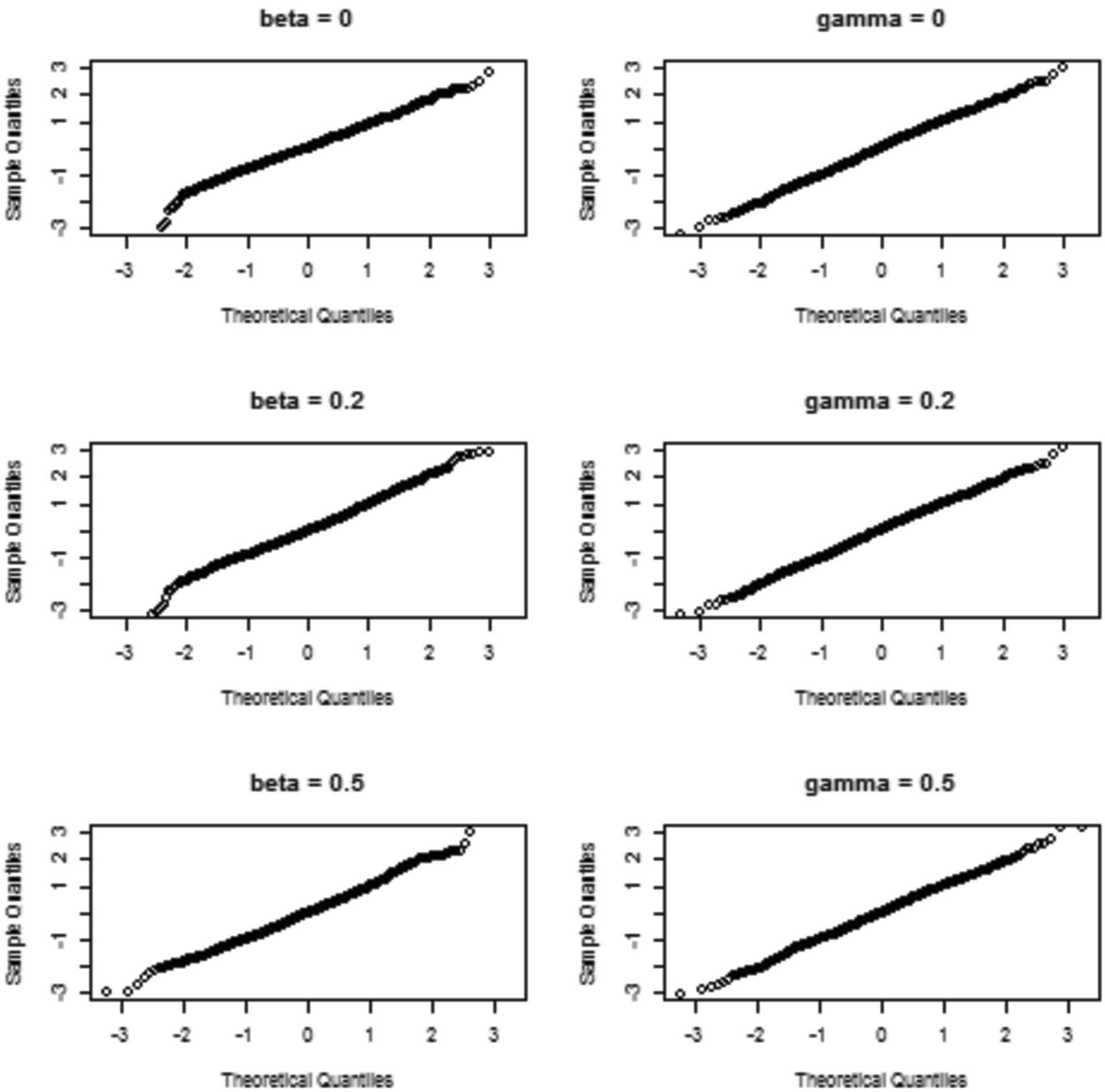

Figure 1. The quantile plots of the standardized $\hat{\beta}$ and $\hat{\gamma}$ against the standard normal.

one may prefer a different model or a different model may fit the data better. In particular, Chen et al. (2012) discussed the same problem when the data arise from the linear transformation model, which is different from the additive hazards model or describes a different type of relationships between the failure time of interest and covariates. Of course, there exist many other possible models that have been discussed or investigated for failure time data but not for the types of data discussed here (Kalbfleisch and Prentice, 2002).

It is worth noting that in the estimation procedure proposed in the previous sections, several assumptions have been made. One is that the relationship between the failure time of interest and the informative observation or censoring time can be described through the latent variable b_i, which may not be true in some situations. As pointed out above, an alternative to this is to employ the copula model-based method as in Ma et al. (2015) and Zhao et al. (2015). However, their methods apply only to the situation where the underlying copula model and the association parameter are known. Another assumption used above is model (2) on the informative observation time C_i. However, it is easy to see that it is straightforward to develop a similar estimation procedure if a different model on the C_i's is used. For this, note that for the situation discussed here, one has complete or right-censored data on the C_i's and therefore the infer-

Table 4. Analysis results on both lung and bladder tumors

Type of tumor		k_n							
		3	4	5	6	7	8	9	10
lung	β	0.014	0.011	0.009	0.007	0.003	0.010	0.006	0.014
($n = 617$)	Std$_\beta$	0.019	0.019	0.019	0.020	0.020	0.019	0.020	0.019
	p-value$_\beta$	0.459	0.512	0.655	0.689	0.711	0.579	0.752	0.470
	γ	0.482	0.480	0.479	0.479	0.479	0.48	0.479	0.485
	Std$_\gamma$	0.187	0.187	0.187	0.187	0.187	0.187	0.187	0.188
	p-value$_\gamma$	0.010	0.011	0.010	0.011	0.010	0.011	0.011	0.010
	AIC	490.67	491.53	491.85	492.67	493.46	492.34	494.13	493.94
bladder	β	0.292	0.278	0.282	0.283	0.270	0.285	0.291	0.287
($n = 617$)	Std$_\beta$	0.031	0.029	0.030	0.031	0.029	0.032	0.031	0.030
	p-value$_\beta$	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	γ	0.471	0.470	0.468	0.468	0.470	0.470	0.469	0.471
	Std$_\gamma$	0.189	0.188	0.189	0.190	0.189	0.188	0.189	0.188
	p-value$_\gamma$	0.013	0.013	0.0132	0.013	0.013	0.013	0.013	0.013
	AIC	471.69	472.43	474.81	475.36	474.25	476.19	478.93	477.58

ence on model (2) or any model used for the C_i's is relatively easy.

APPENDIX A. PROOFS OF THE ASYMPTOTIC PROPERTIES OF $\hat{\theta}_N$

In this Appendix, we will sketch the proof of the asymptotic properties of $\hat{\theta}_n$. For this, we will first describe some more notation and the needed regularity conditions. Define the sieve space

$$\Theta_n = \{\theta_n = (\beta', \gamma', \eta, \Lambda_{1n}, \Lambda_2)\} = \mathcal{B} \otimes \mathcal{M}_n{}^1 \otimes \mathcal{M}^2,$$

where $\mathcal{B}$ is a compact set in R^{2p+1},

$$\mathcal{M}_n{}^1 = \{\Lambda_{1n}(t) = \sum_{l=1}^{s+k_n} \alpha_l I_l(t), \quad \sum_{l=1}^{s+k_n} |\alpha_l| \le K_1, \;\; t \in [0, \tau_c]\},$$

and

$$\mathcal{M}^2 = \{\Lambda_2(t) : 1/K2 \le \Lambda_2(t) \le K_2, \quad t \in [0, \tau_c]\}$$

with K_1 and K_2 being some positive constants, where τ_c is the upper bound of the observation times C_i^*'s. Let $\| \, . \, \|_2$ denote the L^2 norm and $\theta_0 = (\beta_0', \gamma_0', \eta_0, \Lambda_{10}, \Lambda_{20})$ the true value of θ. Also define $d(\theta, \theta_0) = (\| \Lambda_1 - \Lambda_{10} \|_2^2 + \| \Lambda_2 - \Lambda_{20} \|_2^2 + \| \beta - \beta_0 \|_E^2 + \| \gamma - \gamma_0 \|_E^2 + \| \eta - \eta_0 \|_E^2)^{1/2}$, $\mathrm{P}f = \int f(x) dP(x)$, and $\mathrm{P}_n f = n^{-1} \sum_{i=1}^{n} f(X_i)$ for a function f and a probability function P.

To prove the asymptotic properties, we need the following regularity conditions.

(A1.) The covariates Z_i's have a bounded support.

(A2.) The m-th derivative of $\Lambda_k(.)$, denoted by $\Lambda_k^{(m)}(.)$, is Holder continuous such that $|\Lambda_k^{(m)}(t_1) - \Lambda_k^{(m)}(t_2)| \le M |t_1 - t_2|^\omega$ for some $\omega \in (0, 1]$ and all $t_1, t_2 \in (l, u)$, $\quad k = 1, 2$, where $0 < l < u < \infty$ and M are some constants.

(A3.) Let $l(\theta, O)$ denote the log likelihood function based on the observed data $O = (C^*, \Delta, \delta, Z)$, and for any positive number ϵ, we have that $\inf_{d(\theta,\theta_0)<\epsilon} \mathrm{P}l(\theta, O) > \mathrm{P}l(\theta_0, O)$.

(A4) The matrix Σ is finite and positive definite, where Σ is the semi-parametric efficiency bound defined below.

Suppose that the regularity conditions above hold. First we will show that as $n \to \infty$, $\hat{\beta}$ and $\hat{\gamma}$ are strongly consistent and we have

(11)
$$\| \hat{\Lambda}_{1n} - \Lambda_{10} \|_2 \to 0, \quad \| \hat{\Lambda}_2 - \Lambda_{20} \|_2 \to 0, \quad \text{almost surely}$$

and

(12)
$$\| \hat{\Lambda}_{1n} - \Lambda_{10} \|_2 + \| \hat{\Lambda}_2 - \Lambda_{20} \|_2 = O_p(n^{-(1-v)/2} + n^{-rv}).$$

For this, we will verify the conditions given in the Theorem 5.7 of van Der Vaart (1998).

First we will verify the condition

$$J_1 =: \lim_n \sup_{\theta_n \in \Theta_n} |\mathrm{P}_n l(\theta, O) - \mathrm{P}l(\theta, O)| = o_p(1).$$

Note that

$$J_1 \le \lim_n \sup_{\theta_n \in \Theta_n} |\mathrm{P}_n l(\theta, O) - \mathrm{P}l(\theta_n, O)|$$
$$+ \lim_n \sup_{\theta_n \in \Theta_n} |\mathrm{P}l(\theta_n, O) - \mathrm{P}l(\theta, O)| =: J_{11} + J_{12}$$

Therefore, it is sufficient to prove that $J_{1k} = o_p(1), k = 1, 2$. To prove that $J_{11} = o_p(1)$, we just need verify that $\varepsilon = \{l(\theta_n, O), \theta_n \in \Theta_n\}$ is Euclidean class for its envelope function $\max_{\theta_n \in \Theta_n} l(\theta_n, O)$. According to (A1), (A2) and Lemma 2.14 in Pakes and Pollard (1989), it is easy to see that class ε is a Euclidean class. Hence, we have

$J_{11} = o_p(1)$. For J_{12}, by Lemman A1 of Lu et al. (2007) and contiguous property of log-likelihood function, we have $J_{12} = o_p(1)$. Thus, we could obtain that condition $J_1 =: \lim_n \sup_{\theta_n \in \Theta_n} |\mathrm{P}_n l(\theta, O) - \mathrm{P} l(\theta, O)| = o_p(1)$ holds.

To derive the convergence rate, for any $\omega > 0$, define the class $\mathcal{F}_w = \{l(\theta_{n0}, O) - l(\theta, O) : \theta \in \Theta_n, d(\theta, \theta_{n0}) \leq w\}$ with $\theta_{n0} = (\beta_0, \gamma_0, \eta_0, \Lambda_{1n0}, \Lambda_{20})$. Following the calculation of Shen and Wong (1994, P.597), we can establish that $\log N_{[]}(\epsilon, \mathcal{F}_\omega, \| \, . \, \|_2) \leq CN \log(\omega/\epsilon)$ with $N = 2(s + k_n)$, where $N_{[]}(\epsilon, \mathcal{F}_\omega, d)$ denotes the bracketing number (see the Definition 2.1.6 in Van Der Vaart and Wellner, 1996) with respect to the metric or semi-metric d of a function class $\mathcal{F}$. Moreover, some algebraic calculations lead to $\| \, l(\theta_{n0}, O) - l(\theta, O) \, \|_2^2 \leq C\omega^2$ for any $l(\theta_{n0}, O) - l(\theta, O) \in \mathcal{F}_\omega$. Therefore, by Lemma 3.4.2 of Van Der Vaart and Wellner (1996), we obtain

$$\begin{aligned} & E_p \, \| \, n^{1/2}(P_n - P) \, \|_{\mathcal{F}_\omega} \\ & \leq C J_\omega(\epsilon, \mathcal{F}_\omega, \| \, . \, \|_2)\{1 + \frac{J_\omega(\epsilon, \mathcal{F}_\omega, \| \, . \, \|_2)}{\omega^2 n^{1/2}}\}, \ (S) \end{aligned}$$

where $J_\omega(\epsilon, \mathcal{F}_\omega, \| \, . \, \|_2) = \int_0^\omega \{1 + log N_{[]}(\epsilon, \mathcal{F}_\omega, \| \, . \, \|_2)\}^{1/2} d\epsilon \leq CN^{1/2}\omega$. The right-hand side of (S) yield $\phi_n(\omega) = C(N^{1/2}\omega + N/n^{1/2})$. It is easy to see that $\phi_n(\omega)/\omega$ decreases in ω, and $r_n^2 \phi_n(1/r_n) = r_n N^{1/2} + r_n^2 N/n^{1/2} < 2n^{1/2}$, where $r_n = N^{-1/2} n^{1/2} = n^{(1-v)/2}$ with $0 < v < 0.5$. Hence, $n^{(1-v)/2} d(\hat{\theta} - \theta_{n0}) = O_p(1)$ by Theorem 3.2.5 of Van Der Vaart and Wellner (1996). This, together with $d(\theta_{n0}, \theta_0) = O_p(n^{-rv})$ (Lemma A1 in Lu et al. (2007)), yields that $d(\hat{\theta}, \theta_0) = O_p(n^{-(1-v)/2} + n^{-rv})$. The choice of $v = 1/(1+2r)$ yields that rate of convergence of $d(\hat{\theta}_n, \theta_0) = O_p(n^{-\frac{r}{1+2r}})$.

Now we will show that

$$\sqrt{n} b'((\hat{\beta} - \beta_0)', (\hat{\gamma} - \gamma_0)')' \to N(0, \Sigma) \tag{13}$$

and $\hat{\beta}$ and $\hat{\gamma}$ are semi-parametric efficient, where b is any $2p$-dimensional vector. Denote V as the linear span of $\Theta_0 - \theta_0$, where Θ_0 denotes the true parameter space. Let $l(\theta, O)$ be the log-likelihood for a sample of size one and $\delta_n = (n^{-(1-v)/2} + n^{-rv})$. For any $\theta \in \{\theta \in \Theta_0 : d(\theta, \theta_0) = O_p(\delta_n)\}$, define the first order directional derivative of $l(\theta, O)$ at the direction $v \in V$ as

$$\dot{l}(\theta)[v] = \frac{dl(\theta + tv, O)}{dt}|_{t=0}.$$

According to the proof of Theorem 1 of Shen (1997) that

$$\begin{aligned} & b'((\hat{\beta} - \beta_0)', (\hat{\gamma} - \gamma_0)) + \int_0^{\tau_c} g(t) d(\hat{\Lambda}_2(t) - \Lambda_{20}(t)) \\ & \qquad = \frac{1}{n} \sum_{i=1}^n \dot{l}(\theta_0, O_i)[v^*] + o_p(n^{-1/2}), \end{aligned}$$

where b is any $(2p+1)$-dimensional vector with $||b||_E \leq 1$, g is a function with bounded variation on $[0, \tau_c]$, v^* can be given by using Riesz representation theorem as done by Shen (1997). It then follows from the central limits theorem that we have $b'((\hat{\beta} - \beta_0)', (\hat{\gamma} - \gamma_0)) + \int_0^{\tau_c} g(t) d(\hat{\Lambda}_2(t) - \Lambda_{20}(t)) = \frac{1}{n} \sum_{i=1}^n \dot{l}(\theta_0, O_i)[v^*] + o_p(n^{-1/2})$ converges to $N(0, \Sigma)$ in distribution. The semi-parametric efficiency can be established by using the result of Bickel and Kwon (2001) or Theorem 4 in Shen (1997).

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